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Pulmonary Arterial Enlargement and Acute Exacerbations of COPD

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Abstract

BACKGROUND—Exacerbations of chronic obstructive pulmonary disease (COPD) are associated with accelerated loss of lung function and death. Identification of patients at risk for these events, particularly those requiring hospitalization, is of major importance. Severe pulmonary hypertension is an important complication of advanced COPD and predicts acute exacerbations, though pulmonary vascular abnormalities also occur early in the course of the disease. We hypothesized that a computed tomographic (CT) metric of pulmonary vascular disease (pulmonary artery enlargement, as determined by a ratio of the diameter of the pulmonary artery to the diameter of the aorta [PA:A ratio] of >1) would be associated with severe COPD exacerbations.

METHODS—We conducted a multicenter, observational trial that enrolled current and former smokers with COPD. We determined the association between a PA:A ratio of more than 1 and a history at enrollment of severe exacerbations requiring hospitalization and then examined the usefulness of the ratio as a predictor of these events in a longitudinal follow-up of this cohort, as well as in an external validation cohort. We used logistic-regression and zero-inflated negative binomial regression analyses and adjusted for known risk factors for exacerbation.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

RESULTS—Multivariate logistic-regression analysis showed a significant association between a PA:A ratio of more than 1 and a history of severe exacerbations at the time of enrollment in the trial (odds ratio, 4.78; 95% confidence interval [CI], 3.43 to 6.65; P<0.001). A PA:A ratio of more than 1 was also independently associated with an increased risk of future severe exacerbations in both the trial cohort (odds ratio, 3.44; 95% CI, 2.78 to 4.25; P<0.001) and the external validation cohort (odds ratio, 2.80; 95% CI, 2.11 to 3.71; P<0.001). In both cohorts, among all the variables analyzed, a PA:A ratio of more than 1 had the strongest association with severe exacerbations.

CONCLUSIONS—Pulmonary artery enlargement (a PA:A ratio of >1), as detected by CT, was associated with severe exacerbations of COPD. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov numbers, NCT00608764 and NCT00292552.)

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are critical events in the natural history of the disease and are associated with accelerated loss of lung function and poor quality of life.[1,2] Hospitalizations for exacerbations account for $18 billion in direct costs annually in the United States and are associated with 1-year mortality of 21% and 5-year mortality of 55%.[3] Identification of patients at risk for these events is therefore of major importance.

Acute exacerbations of COPD are defined as an increase in dyspnea, cough, or sputum production warranting a change in therapy. These acute exacerbations often result from the acquisition of new strains of bacteria, viral infection, or exposure to pollution.[3,4] In addition to these triggers, it is clear that patients with COPD may have an increase in respiratory symptoms owing to overt or subclinical cardiovascular events including ischemia,[5] heart failure,[6] and thromboembolism,[7] the latter of which causes up to 25% of severe exacerbations.[7]

Our ability to identify patients at risk for exacerbations was improved by the findings in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study,[8] which showed the predictive usefulness of clinical characteristics such as prior exacerbations. However, the factors identified in that study explain only a minority of the variability in risk, and better tools are needed, particularly for predicting exacerbations requiring hospitalization.

Pulmonary vascular disease is an important risk factor for exacerbations and death.[9-11] Computed tomography (CT) can be used to measure the diameter of the pulmonary artery and the ratio of the diameter of the pulmonary artery to the diameter of the aorta (PA:A ratio) — both of which correlate with results from invasive measures of pulmonary artery pressure.[12-14] We hypothesized that a PA:A ratio of more than 1 would be associated with a history of severe acute exacerbations of COPD at the time of enrollment in the current trial, the COPDGene trial, and would be independently associated with the risk of subsequent events in both the COPDGene longitudinal cohort and a validation cohort from the ECLIPSE trial.

METHODS

STUDY POPULATIONS

We enrolled in the COPDGene study persons 45 to 80 years of age who were current or former smokers, with a history of 10 pack-years or more of cigarette smoking. Participants were recruited from 21 U.S. clinical centers. The COPDGene study was approved by the institutional review board at each participating center, and all participants in both studies provided written informed consent. The first author assumes responsibility for the accuracy and completeness of all the data and analyses. In an effort to identify genetic factors associated with COPD,[15] participants underwent prebronchodilator and postbronchodilator

spirometry, 6-minute-walk testing, and whole-lung chest CT and completed questionnaires regarding symptoms (see additional details in the complete description of the methods in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The COPDGene study enrolled a total of 10,300 persons; we included in this analysis the 3464 participants who had Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II to IV COPD[1] (with stages ranging from I to IV and higher stages indicating more severe disease) and for whom there were verified data that included quantitative CT analysis (airway data were available for 1321 persons). Of these patients, 2985 (86%) participated in a longitudinal follow-up study (median length of follow-up, 2.1 years) to prospectively track their clinical course, including the development of exacerbations, with the use of an automated telephone system and personal telephone calls from the clinical coordinator.[16]

The ECLIPSE study was a 3-year longitudinal study with the objective of identifying surrogate end points, including biomarkers and CT scan measures, that were associated with disease progression and exacerbations in persons with various COPD subtypes. Details regarding the ECLIPSE cohort and protocol have been published previously.[8,17] The current analysis included the 2005 ECLIPSE participants who completed 3 years of follow-up and who had a baseline CT scan available for interpretation, as well as the clinical data necessary for multivariate modeling of exacerbation risk (see below).

DETERMINATION OF EXACERBATION

Acute exacerbations of COPD were self-reported in both the COPDGene and ECLIPSE studies. These episodes were defined and quantified in both trials by answers to questions in a respiratory epidemiology questionnaire modified from the Epidemiology Standardization Project questionnaire (American Thoracic Society–Division of Lung Diseases [ATS-DLD]-78).[18] The details of the methods in the COPDGene study are provided in the Supplementary Appendix. In both the ECLIPSE and COPDGene longitudinal follow-up studies, participants were recorded as having a severe exacerbation if they had increased dyspnea, cough, or sputum production and required admission to the hospital for treatment. Mild-to-moderate exacerbations were defined by similar symptoms that were treated with antibiotics or systemic glucocorticoids in the outpatient setting or during an emergency room visit. The occurrence and frequency of all exacerbations (mild-to-moderate and severe) were analyzed as secondary end points.

IMAGING

For participants in the COPDGene trial, analysis of the lung parenchyma and airways was performed on volumetric CT scans of the chest obtained without the administration of contrast material. Parenchymal analysis was performed with the use of the Slicer software package (www.Slicer.org), and airway analysis was performed with the use of Volumetric Information Display and Analysis (VIDA) Pulmonary Workstation 2 software (www.vidadiagnostics.com). Emphysema was defined by a CT attenuation value of less than –950 Houns-field units on inspiratory scans, and gas trapping was defined by a CT attenuation of less than –856 Hounsfield units on expiratory scans. We assessed airway disease by measuring the wall-area percent ([the bronchial wall area ÷ total cross-sectional area of the wall and lumen] × 100), using the average of six fourth-generation airways, as reported previously.[19]

Vascular measurements in the COPDGene and ECLIPSE cohorts were performed on baseline CT scans by an investigator who was unaware of the participants' clinical characteristics. Measurements were made from axial CT images with the use of inspiratory acquisitions with digital imaging and communications in medicine (DICOM) software

(OsiriX DICOM Viewer, version 4.0, 32-bit; www.osirix-viewer.com). The interpreter measured the diameter of the main pulmonary artery at the level of its bifurcation and measured the diameter of the ascending aorta in its maximum dimension using the same images, as shown in Figure 1.

STATISTICAL ANALYSIS

Baseline data from the COPDGene cohort are expressed as means with standard deviations for normally distributed values. Bivariate analyses were conducted with the use of a two-tailed Fisher's exact test for categorical data and two tailed t-tests or a Wilcoxon rank-sum test for continuous data when appropriate. Cohen's kappa was calculated to identify the intraobserver and interobserver agreement for the presence of a PA:A ratio of more than 1. Univariate logistic regression was used to determine the associations between patient characteristics (including the PA:A ratio) and the occurrence of a severe exacerbation of COPD in the year before enrollment in the COPDGene trial.

The independent variables that were studied are listed in Table S4 in the Supplementary Appendix. Variables showing a univariate association with severe exacerbations (at $P<0.10$) were included in stepwise backward multivariate logistic models to adjust for confounders. In an effort to prospectively validate the association of the PA:A ratio with future severe exacerbations, we then examined the relationship between a PA:A ratio of more than 1 and these events as reported in the COPDGene longitudinal follow-up data set and the ECLIPSE cohort, using separate multivariate logistic-regression and zero-inflated negative binomial models. These models included variables previously reported to be independently associated with acute exacerbations of COPD in the ECLIPSE study[8]: gastroesophageal reflux disease (GERD), lower values for the forced expiratory volume in 1 second (FEV_1), a history of acute exacerbations of COPD within the previous year, increased white-cell count, and decreased quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) score (which ranges from 0 to 100, with higher scores indicating worse quality of life and with a minimal clinically important difference of 4 points). Similar models for the prediction of all exacerbations were also developed. All analyses were performed with the use of SPSS software, version 20.0, and P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

CHARACTERISTICS OF PATIENTS IN THE COPDGene STUDY

Of the 3690 patients with GOLD stage II to COPD who were enrolled, 3464 (94%) had complete CT scan data available for analysis. Patients were divided into two groups on the basis of the PA:A ratio (PA:A ratio of ≤1 or PA:A ratio of >1), with a PA:A ratio of more than 1 considered indicate the presence of relative pulmonary artery enlargement.[12-14] The kappa values for intraobserver and interobserver agreement for detecting a PA:A ratio of more than 1 were 0.92 (95% confidence interval [CI], 0.83 to 1.0) and 0.75 (95% CI, 0.67 to 0.82), respectively. As compared with the group that had a PA:A ratio of 1 or lower, the group with a PA:A ratio of more than 1 included larger numbers of women and more blacks and had a higher mean body-mass index; higher rates of asthma, congestive heart failure, thromboembolic disease, sleep apnea, GERD, and use of supplemental oxygen; poorer lung function; and more severe pulmonary symptoms as measured by scores on the SGRQ and the modified Medical Research Council (MRC) questionnaire (in which scores range from 0 to 4, with higher scores indicating greater dyspnea) (Table 1). The group with a PA:A ratio of more than 1 had a larger percentage of lung volume with emphysema on CT and a larger fourth-generation bronchial wall-area percent, but the two groups had similar levels of gas trapping. Additional information about the relationships between clinical characteristics and

a PA:A ratio of more than 1 is provided in Tables S2 and S3 in the Supplementary Appendix.

ASSOCIATION BETWEEN PA:A RATIO AND SEVERE EXACERBATIONS AT STUDY ENROLLMENT

More patients with a PA:A ratio of more than 1 than those with a PA:A ratio of 1 or less reported a severe exacerbation in the year before enrollment (53% vs. 13%; odds ratio, 7.44; 95% CI, 6.23 to 8.89; P<0.001). We also found significant univariate associations between severe exacerbations and younger age, black race, use of supplemental oxygen, congestive heart failure, sleep apnea, thromboembolic disease, GERD, asthma, chronic bronchitis, employment in a hazardous job (one in which the person was exposed to dusts or volatile chemicals), and multiple markers of disease severity as outlined in Table S4 in the Supplementary Appendix. In univariate models, increased diameter of the pulmonary artery, increased percentage of lung volume with emphysema on CT, increased fourth-generation wall-area percent, and gas trapping were also associated with severe exacerbations. Multiple logistic-regression analyses showed continued significant independent associations between severe exacerbations and younger age, lower FEV_1 values, higher score on the SGRQ, and a PA:A ratio of more than 1 (odds ratio, 4.78; 95% CI, 3.43 to 6.65; P<0.001) (Table 2).

USEFULNESS OF THE PA:A RATIO IN PREDICTING FUTURE SEVERE EXACERBATIONS

Univariate logistic-regression analyses revealed that a PA:A ratio of more than 1 was associated with severe exacerbations in the longitudinal follow-up cohort of the COPDGene trial (odds ratio, 4.56; 95% CI, 3.73 to 5.58; P<0.001), and similar results were observed when univariate zero-inflated negative binomial regression was used to model the frequency of these events (an increase in frequency by a factor of 3.68; 95% CI, 3.45 to 3.91; P<0.001). Multivariate modeling revealed that a PA:A ratio of more than 1 was associated with future severe exacerbations after adjustment for factors that were shown to be important both in the baseline COPDGene analysis and in the ECLIPSE study (age, presence of GERD, FEV_1 values, score on the SGRQ, and prior exacerbations). As shown in Table 2, a PA:A ratio of more than 1 remained significantly associated with severe exacerbations in this model (odds ratio, 3.44; 95% CI, 2.78 to 4.25; P<0.001), whereas the associations with age and with the presence of GERD were no longer significant. Multivariate zero-inflated negative binomial regression confirmed that a PA:A ratio of more than 1 was independently associated with an increased frequency of severe exacerbations (an increase by a factor of 2.99; 95% CI, 2.77 to 3.21; P<0.001). When we evaluated the relationship between values for the PA:A ratio and the risk of severe exacerbation, we observed a distinct increase in the occurrence of severe exacerbations at a PA:A threshold of 1, as shown in Figure 2.

VALIDATION OF THE ASSOCIATION OF A PA:A RATIO OF MORE THAN 1 WITH SEVERE EXACERBATIONS

A univariate logistic-regression analysis of data from the ECLIPSE cohort showed that a PA:A ratio of more than 1 was associated with severe exacerbations at 1 year (odds ratio, 4.12; 95% CI, 3.20 to 5.31; P<0.001) and at 3 years (odds ratio, 4.82; 95% CI, 3.92 to 5.93; P<0.001). In multivariate logistic models, a PA:A ratio of more than 1 was the factor that had the strongest association with severe exacerbations at both time points (odds ratio, 2.8; 95% CI, 2.11 to 3.71; P<0.001 at 1 year; and odds ratio, 3.81; 95% CI, 3.04 to 4.78; P<0.001 at 3 years) (Table 3). Separate multivariate zero-inflated binomial regression models confirmed that a PA:A ratio of more than 1 was associated with an increased frequency of severe exacerbations at 1 year (an increase by a factor of 2.03; 95% CI, 1.61 to 2.55; P<0.001).

ASSOCIATION BETWEEN PA:A RATIO AND ALL EXACERBATIONS

In multivariate regression analyses of data from the COPDGene longitudinal follow-up cohort, the presence of an elevated PA:A ratio was also associated with an increase in the occurrence of any exacerbation (odds ratio, 1.86; 95% CI, 1.54 to 2.24; P<0.001) (Table 2), as well as in the frequency of these events (an increase by a factor of 1.62; 95% CI, 1.47 to 1.78; P<0.001). In the ECLIPSE validation cohort, a PA:A ratio of more than 1 was associated with all exacerbations at 1 year and at 3 years (odds ratio, 2.17; 95% CI, 1.71 to 2.74; P<0.001 at 1 year; and odds ratio, 6.68; 95% CI, 4.47 to 9.96; P<0.001 at 3 years) (Table 3). At 3 years, this association was stronger than that with other components of the model — stronger than the association with an exacerbation in the previous year and stronger than the association with the SGRQ score and white-cell count, neither of which was significantly associated at that time point. Multivariate zero-inflated binomial regression models confirmed that a PA:A ratio of more than 1 was independently associated with an increase in the frequency of all exacerbations at 1 year in the ECLIPSE cohort (an increase by a factor of 1.43; 95% CI, 1.29 to 1.60; P<0.001). Although a PA:A ratio of more than 1 was associated with all exacerbations and with severe exacerbations, it was not independently associated with mild-to-moderate events.

DISCUSSION

We found that a PA:A ratio of more than 1 at baseline was associated with future exacerbations of COPD, particularly those requiring hospitalization. Although prior studies have shown correlations between pulmonary hypertension and acute exacerbations of COPD, we examined the relationship between exacerbations and a readily available CT measure of pulmonary vascular disease. The PA:A ratio also appears to outperform many established risk factors for exacerbation including GERD,[8] SGRQ score,[8] breathlessness,[11] chronic bronchitis,[20] and FEV_1,[8] as well as recently identified CT predictors.[19]

Many patients who present with increased dyspnea, cough, or sputum production consistent with a diagnosis of acute exacerbations of COPD actually have a poor outcome as a result of clinically apparent as well as undiagnosed cardiac disease.[5-7] Though congestive heart failure, sleep apnea, and thromboembolic disease were not independently associated with exacerbations, the value of the PA:A ratio may be due in part to its capacity to identify patients who have pulmonary vascular disease as a result of these disorders and who are at particular risk for cardiovascular triggers of exacerbation. An elevated PA:A ratio may also identify patients with pulmonary vascular disease resulting from underlying emphysema and limited capacity to accommodate the additional ventilation–perfusion mismatch and increased oxygen demand associated with many causes of acute exacerbations of COPD.[21,22]

Increased size of the pulmonary artery on CT could be the result of several pathologic processes, including resting pulmonary hypertension (see echocardiographic data in the Supplementary Appendix), peripheral vascular pruning with centralization of blood flow, undiagnosed cardiovascular disease, or a combination of these mechanisms.[21,23-26] In addition, local inflammation is associated with endothelial dysfunction and regional vascular changes, even in patients with mild airflow obstruction.[25-29] Future studies could be designed to test antiinflammatory agents, including statins, azithromycin, and roflumilast, as targeted therapy for exacerbation-prone patients with a PA:A ratio of more than 1.[30-33]

Our study is limited by its observational design, and thus we cannot definitively conclude that elevations in the PA:A ratio cause acute exacerbations of COPD or that these results would apply to other populations. However, validation of the PA:A ratio as a predictor of severe and all exacerbations in the ECLIPSE cohort strengthens our findings considerably.

CT-detected pulmonary artery enlargement (a PA:A ratio of >1) is independently associated with acute exacerbations of COPD and identifies a sub-population at high risk for hospitalization for these events. The metric is particularly valuable given that the measurement of this ratio requires minimal training and, when measured at the pulmonary artery bifurcation, appears to be reproducible. The measurement can also be made from routine CT images that were obtained without the use of vascular contrast material or the use of special software. Furthermore, the PA:A ratio, as compared with the pulmonary artery diameter alone, allows for adjustment for anthropometric differences between patients, corrects for CT acquisition and reconstruction algorithms, and provides an internal control that allows the ratio to be compared over time and across cohorts, a feature not shared by other CT markers of exacerbation risk.[19]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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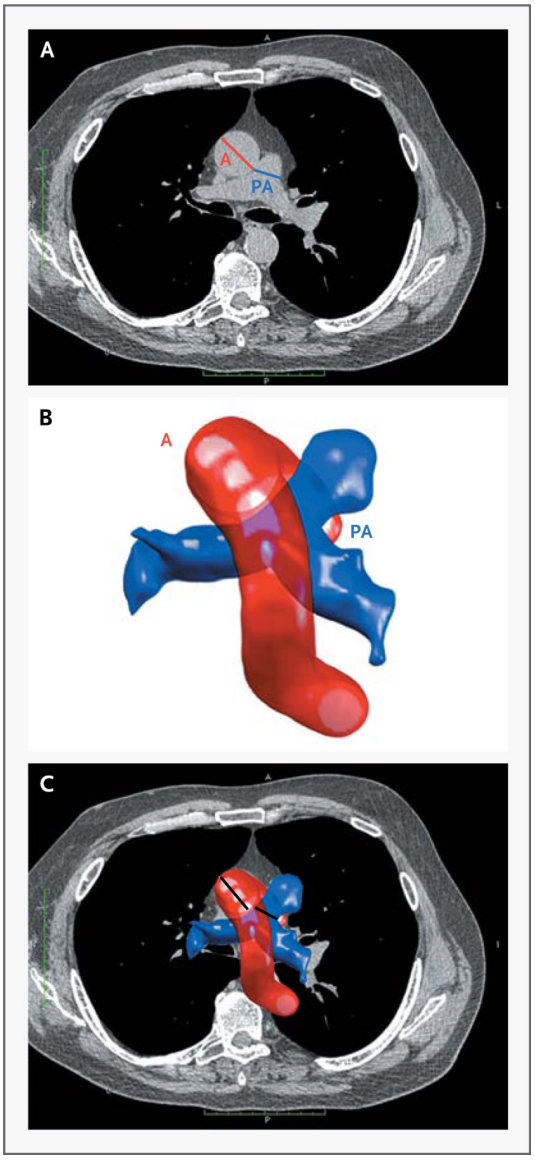

Figure 1. Measurement of the Diameters of the Pulmonary Artery and Aorta

Panel A shows an axial chest computed tomographic (CT) image at the level of the left and right main pulmonary arteries, obtained without the administration of contrast material. Measurements of the diameter of the main pulmonary artery (PA) and the diameter of the aorta (A) at the level of the bifurcation were used to calculate the PA:A ratio. In cases in which A was not uniform in diameter, two measurements were taken 90 degrees apart, and the larger diameter was used. Panel B is a digital three-dimensional reconstruction, in axial cross section, of the great vessels that shows the spatial relationship between PA and A. In Panel C, the three-dimensional reconstruction is overlaid on the axial CT image.

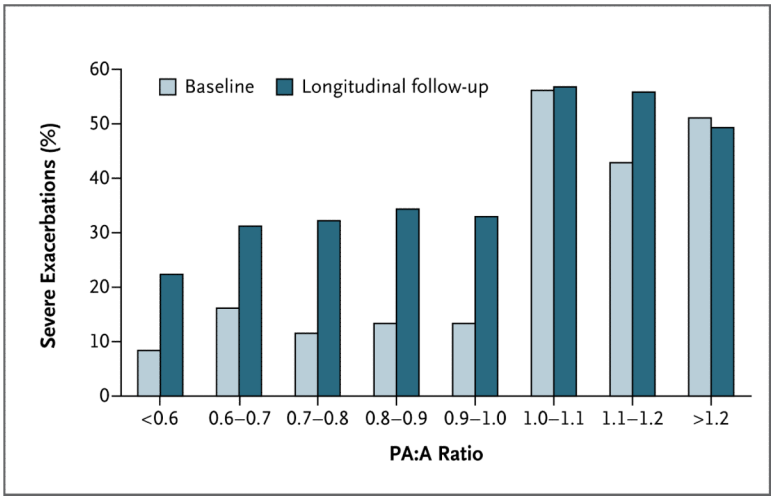

Figure 2. Relationship between the PA:A Ratio and Severe Exacerbations at Baseline and during Follow-up

A histogram shows the relationship between the PA:A ratio and the occurrence of severe exacerbations (those requiring hospitalization) at baseline and during follow-up in the COPDGene study. The rate of severe exacerbations of COPD is shown according to increments of 0.1-unit changes in the absolute PA:A ratio. The risk of severe exacerbation increased at a threshold PA:A ratio of 1. A similar pattern was observed in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) validation cohort.

Table 1

Baseline Characteristics of the Patients.*

Variable	PA:A Ratio ≤1 (N = 2645)	PA:A Ratio >1 (N = 819)	P Value
Age (yr)	64±9	63±9	0.003
Male sex (%)	60	42	<0.001
Non-Hispanic white race (%)†	81	67	<0.001
GOLD stage (%)‡			
II	56	43	<0.001
III	30	36	0.004
IV	14	21	<0.001
Body-mass index§	28±6	29±7	<0.001
Hypertension (%)	50	53	0.08
Asthma (%)	25	34	<0.001
Smoking history (pack-yr)	54±28	50±25	0.001
Current smoker (%)	43	36	<0.001
Congestive heart failure (%)	4	9	<0.001
Thromboembolic disease (%)	5	9	<0.001
Sleep apnea (%)	16	22	<0.001
Gastroesophageal reflux disease (%)	30	34	0.03
Supplemental oxygen use (%)	22	44	<0.001
Distance covered on 6-min walk (ft)	1204±415	983±450	<0.001
Total score on SGRQ¶	38±22	48±21	<0.001
Score on modified MRC‖	2±1	3±1	<0.001
FEV_1 (% of predicted value)	52±18	46±18	<0.001
FVC (% of predicted value)	78±17	73±18	<0.001
FEV_1:FVC ratio	0.50±0.13	0.48±0.13	<0.001
Diameter of aorta (cm)	3.27±0.38	3.09±0.35	<0.001
Diameter of pulmonary artery (cm)	2.75±0.37	3.33±0.42	<0.001
Percent of lung volume with emphysema on CT	12.6±12.5	14.0±13.1	0.01
Percent of lung volume with gas trapping on CT	38.7±20.7	40±20.6	0.14
Fourth-generation wall area percentage	65.5±2.4	66.2±2.2	<0.001
Frequency of exacerbations in previous year	0.59±1.09	1.21±1.48	<0.001

*Plus–minus values are means ±SD. Baseline characteristics are shown according to the ratio of the diameter of the pulmonary artery (PA) to the diameter of the aorta (A). There were no significant differences between the groups with respect to the following variables: the presence of chronic bronchitis, coronary artery disease, peripheral vascular disease, or cerebrovascular disease or working at a hazardous job, which was defined as one in which the person was exposed to dusts or volatile chemicals. CT denotes computed tomography, FEV_1 forced expiratory volume in 1 second, and FVC forced vital capacity.

†Race was self-reported.

‡Symptoms of chronic obstructive pulmonary disease were assessed with the use of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging, in which stages range from I to IV, with higher stages indicating more severe symptoms.

§The body-mass index is the weight in kilograms divided by the square of the height in meters.

[¶] Scores on the St. George's Respiratory Questionnaire (SGRQ) range from 0 to 100, with higher scores indicating worse quality of life; the minimal clinically important difference is 4.

[‖] Scores on the modified Medical Research Council questionnaire (MRC) range from 0 to 4, with higher scores indicating greater dyspnea.

Table 2

Factors Independently Associated with Exacerbations at Enrollment and Follow-up.*

Time Period and Factor	Odds Ratio (95% CI)	P Value
History of severe exacerbations at enrollment		
FEV_1, per percentage-point decrease	1.02 (1.01–1.03)	0.001
SGRQ, per 1-point increase	1.03 (1.02–1.04)	<0.001
Age, per 1-year increase	0.97 (0.95–0.99)	0.002
PA:A ratio >1	4.78 (3.43–6.65)	<0.001
Severe exacerbations during longitudinal follow-up		
Exacerbation in previous yr	2.01 (1.61–2.49)	<0.001
FEV_1, per percentage-point decrease	1.02 (1.01–1.03)	<0.001
SGRQ, per 1-point increase	1.02 (1.01–1.02)	<0.001
GERD	1.22 (0.98–1.52)	0.08
Age, per 1-yr increase	0.99 (0.99–1.01)	0.74
PA:A ratio >1	3.44 (2.78–4.25)	<0.001
All exacerbations during longitudinal follow-up		
Exacerbation in previous yr	2.49 (2.09–2.96)	<0.001
FEV_1, per percentage-point decrease	1.02 (1.01–1.03)	<0.001
SGRQ, per 1-point increase	1.01 (1.01–1.02)	<0.001
GERD	1.75 (1.47–2.08)	<0.001
Age, per 1-yr increase	1.01 (0.99–1.01)	0.83
PA:A ratio >1	1.86 (1.54–2.24)	<0.001

*For the analysis of the associations with a history of severe exacerbation at enrollment, all variables showing a univariate association with severe exacerbations (at P<0.10) were included in the original backward multivariate model. These included age, race, chronic bronchitis, asthma, heart failure, a hazardous job, use of supplemental oxygen, distance covered on a 6-minute-walk test, score on the modified MRC questionnaire, score on the SGRQ, FEV_1 value, a PA:A ratio of more than 1, percentage of lung volume with emphysema on CT, percentage of lung volume with gas trapping on CT, and fourth-generation wall-area percent as detected on CT. With respect to severe exacerbations and all exacerbations during the follow-up period in the longitudinal cohort of the COPDGene study, a multivariate model showing the relationship of the risk of severe exacerbations and all exacerbations with key factors associated with exacerbation risk was derived from variables that contributed significantly to the original retrospective multivariate analysis (age, SGRQ score, FEV_1 value, and PA:A ratio >1), as well as additional factors identified in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study (gastroesophageal reflux disease [GERD] and prior exacerbations). White-cell count was not included in the model because this variable was not assessed in the COPDGene data set.

Table 3

Factors Associated with COPD Exacerbations in the ECLIPSE Validation Cohort, According to the Severity of the Exacerbation and Duration of Follow-up.*

Factor	Year 1		Year 3	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Severe exacerbations				
Exacerbation in previous yr	2.43 (1.80–3.29)	<0.001	1.79 (1.44–2.24)	<0.001
FEV_1, per percentage-point decrease	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	<0.001
SGRQ, per 1-point increase	1.03 (1.02–1.04)	<0.001	1.02 (1.01–1.02)	<0.001
GERD	1.38 (1.01–1.88)	0.41	1.43 (1.12–1.83)	0.004
White-cell count, per $1\times10^3/mm^3$ increase	1.07 (1.01–1.13)	0.01	1.05 (1.01–1.10)	0.03
PA:A ratio >1	2.8 (2.11–3.71)	<0.001	3.81 (3.04–4.78)	<0.001
All exacerbations				
Exacerbation in previous yr	3.78 (3.07–4.65)	<0.001	3.59 (2.76–4.67)	<0.001
FEV_1, per percentage-point decrease	1.02 (1.01–1.02)	<0.001	1.01 (1.01–1.02)	0.001
SGRQ, per 1-point increase	1.01 (1.00–1.01)	0.002	1.00 (0.99–1.01)	0.17
GERD	1.72 (1.36–2.17)	<0.001	1.69 (1.27–2.23)	<0.001
White-cell count, per $1\times10^3/mm^3$ increase	1.05 (0.99–1.09)	0.06	1.01 (0.96–1.06)	0.85
PA:A ratio >1	2.17 (1.71–2.74)	<0.001	6.68 (4.47–9.96)	<0.001

* In a multivariate model, GERD, prior exacerbations, SGRQ score, FEV_1 values, white-cell count, and a PA:A ratio of more than 1 were evaluated for their value in predicting the risk of severe exacerbations and all exacerbations at 1 year and 3 years in a validation cohort from the ECLIPSE study.